Organic LETTERS
Letter
pubs.acs.org/OrgLett

Evidence for the Cyclic CN_2 Carbene in the Gas Phase

Eva Hanzlová,[†,∥] Jiří Váňa,[‡,∥] Christopher J. Shaffer,[§] Jana Roithová,*[,‡] and Tomáš Martinů*[,†]

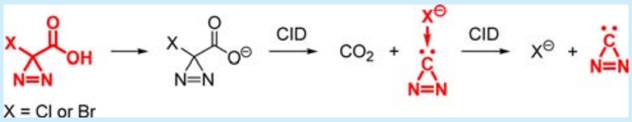
[†]Department of Organic Chemistry, University of Chemical Technology, Technická 5, 166 28 Prague, Czech Republic

[‡]Department of Organic Chemistry, Faculty of Science, Charles University in Prague, Hlavova 2030/8, 128 43 Prague, Czech Republic

[§]Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 166 10 Prague, Czech Republic

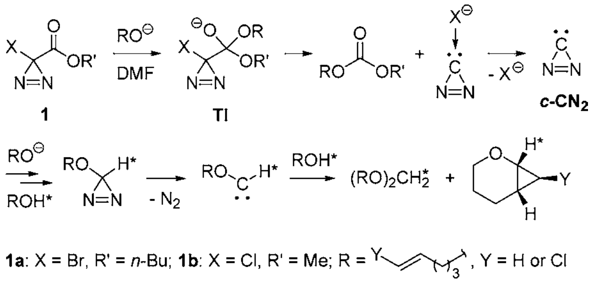
Supporting Information

ABSTRACT: 3-Halodiazirine-3-carboxylic acids (*c*-CN_2XCOOH, X = Cl or Br) were prepared from their esters and converted to the corresponding sodium salts. Collision-induced dissociation (CID) of the carboxylate ions led exclusively to the loss of CO_2 and the resulting *c*-CN_2X^- ions dissociated to *c*-CN_2 carbene at low energies. The bond dissociation energy (BDE) for *c*-CN_2Br^- was found to be less than 8 kcal/mol using CID of the anion generated by electrospray ionization of the carboxylate. The analogous difluoro system ($CF_2XCOOH/CF_2X^-/CF_2$) exhibits similar dissociative behavior. All experimental BDEs are in very good agreement with MP4/aug-cc-pVTZ calculations.



The cyclic CN_2 carbene (diazirinylidene, ***c*-CN₂**) is one of the simplest experimentally elusive reactive intermediates. Despite its formal classification as an N-heterocyclic carbene (NHC), the ground-state singlet ***c*-CN₂** is predicted to be electrophilic and can be considered a single-carbon atom donor due to its potential for the extrusion of N_2.[1] We have found experimental and computational evidence for the intermediacy of ***c*-CN₂** in the reactions of 3-bromo- or 3-chlorodiazirine-3-carboxylates **1** with alkoxide ions in a DMF solution below 0 °C.[1,2] The formation of dialkyl carbonates, dialkoxymethanes, and 2-oxabicyclo[4.1.0]heptanes in these reactions, accompanied by the evolution of N_2, can be explained by a nucleophilic displacement of the corresponding *c*-CN_2X^- ion, readily dissociating to ***c*-CN₂** (Scheme 1). The electrophilic ***c*-CN₂** reacts further with alkoxide ions in the presence of an alcohol, eventually affording an alkoxymethylene, most probably by the denitrogenation of a putative alkoxydiazirine. Final products arise from the alkoxymethylene by an alcohol O−H insertion and intramolecular [2 + 1] cycloaddition (when the alkoxy group carries a suitably positioned and substituted C═C bond). The proposed mechanism is supported by deuterium labeling and a detailed computational study covering the selectivity of the initial nucleophilic displacement, lability of *c*-CN_2X^- ions to dissociation, and basicity and kinetic stability of all proposed intermediates to isomerization.

Scheme 1. Reaction of Esters 1 with Alkoxide Ions



This is the only system available so far for the generation of ***c*-CN₂** in solution. The electrophilic ***c*-CN₂** is scavenged by the strongly nucleophilic environment, hindering attempts at trapping the carbene by [2 + 1] cycloaddition. On the other hand, the cycloaddition of the intermediate alkoxycarbene has to be facilitated by allowing it to proceed in an intramolecular fashion so that it can compete with the fast O−H insertion.

Given the limitations of solution chemistry, we set out to exploit the well-defined conditions of gas phase experiments in order to gain further evidence for the formation of *c*-CN_2X^- ions and ***c*-CN₂** carbene.[3] Initially, we subjected solutions of bromo ester **1a** and chloro ester **1b**, respectively, to electrospray ionization (ESI) and searched for the signals of the corresponding *c*-CN_2X^- ions or the putative tetrahedral intermediate ions (TIs) formed by the nucleophilic addition of an alkoxide or hydroxide to the ester C═O bond (Scheme 1). We have explored the ionization and solvent conditions (methanol, butan-1-ol, acetonitrile, addition of up to 50% v/v water or DMF), but we only observed the corresponding halide ions (free and water-solvated) to be the most abundant fragments within the ESI source. These results may reflect the expected metastability of both *c*-CN_2X^- ions[1] and their parent TIs[4] under the employed conditions.

Therefore, we chose to use an alternative approach to the generation of *c*-CN_2X^- and ***c*-CN₂** avoiding the intermediacy of

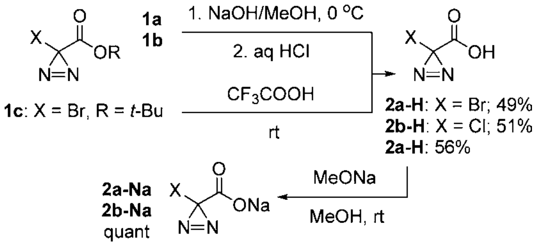
Received: September 18, 2014
Published: October 8, 2014

dx.doi.org/10.1021/ol5027602 | *Org. Lett.* 2014, 16, 5482−5485

TIs, the collision-induced dissociation (CID) of halodiazirine carboxylate ions *c*-CN_2XCOO^- (**2**). Graul and Squires found decarboxylation to be the lowest energy fragmentation pathway in CID of many different $RCOO^-$ ions.[5] Importantly, this process is known to be barrierless and continuously endothermic. The measured bond dissociation energies (BDEs) should thus match the theoretically predicted energy demands for the formation of the separated R^- ions and CO_2. A B3LYP/6-311+g(d) energy scan[6] showed that the dissociation of bromo ion **2a** and chloro ion **2b** to *c*-CN_2X^- and CO_2 is indeed a continuously endothermic process, and calculations at the MP4/aug-cc-pVTZ//MP2/6-311+g(d) level[7,8] predicted the BDEs of 24.5 and 27.8 kcal/mol, respectively. Subsequent dissociation of *c*-CN_2X^- to ***c*-CN$_2$** and X^- (X = Br, Cl) is less endothermic, with calculated BDEs equal to 10.1 and 13.3 kcal/mol, respectively.

We have been able to prepare authentic samples of the corresponding 3-halodiazirine-3-carboxylic acids **2-H** and their sodium salts **2-Na** to be used in our CID experiments (Scheme 2). We obtained the bromo acid **2a-H** by basic hydrolysis of the *n*-butyl ester **1a** in methanol[9] or by dealkylation of the *tert*-butyl ester **1c** with trifluoroacetic acid; the chloro acid **2b-H** can be prepared by hydrolysis of the methyl ester **1b**. Obtained in moderate yields, the novel acids **2-H** (formally trisubstituted derivatives of acetic acid) are colorless low-melting crystalline solids stable for hours at rt.[10] The structural assignment of **2-H** is based on the $^1H/^{13}C$ NMR, IR, and HRMS spectra and reactivity: (a) the quantitative conversion to the highly explosive salts **2-Na** using sodium methoxide in methanol; (b) esterification with butan-1-ol using DCC/DMAP in dichloromethane affording the corresponding *n*-butyl esters (see the Supporting Information (SI)).

Scheme 2. Preparation of Acids 2-H and Salts 2-Na



We studied the structure of the ions generated by ESI from a methanolic solution of the bromo carboxylate **2a-Na** by infrared multiphoton dissociation (IRMPD) spectroscopy.[11] This method provides infrared characteristics of isolated ions in the gas phase.[12,13] The IRMPD spectrum of the generated anions shows two bands at 1700 and 1275 cm^{-1} that correspond well to the predicted C=O (1704 cm^{-1}) and C−C (1268 cm^{-1}) stretching modes of ion **2a** (Figure 1). In comparison, the predicted C−C stretch of the alternative diazo isomer **3a** is suggested to be at significantly lower wavenumbers (1227 cm^{-1}) than found experimentally.

Having confirmed the structure of bromo ion **2a** isolated in the gas phase, we have performed its CID and determined the exact masses of its fragment ions. We have observed that **2a** dissociates CO_2 as expected, resulting in a mixture of CN_2Br^-, Br^-, and H_2OBr^- ions, with no other fragmentations competing (Figure 2a). It should be pointed out that the possibility of denitrogenation of the diazirine ring in **2a** was of concern.[14,15] Analogously, CID of the chloro ion **2b** afforded a mixture of CN_2Cl^- and H_2OCl^- ions[16] containing ca. 5% of the $C_2O_2Cl^-$ ion, possibly formed by the loss of N_2 (Figure 2b). These results attest to the kinetic stability of the CN_2 ring to opening in our experiments as we have pointed out previously for our chemistry in solution.[1b]

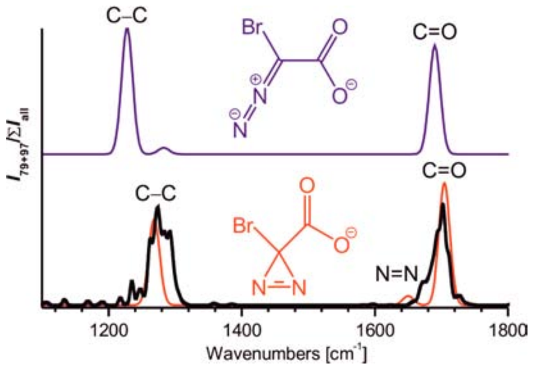


Figure 1. IRMPD spectrum of an anion generated by ESI from methanolic solution of **2a-Na** (black line) and its comparison with the theoretical B3LYP/6-311+G(d) IR spectra (lines represent the theoretical spectra folded with the Gaussian function with full width at half-maximum of 10 cm^{-1}) calculated for **2a** (red line) and **3a** (blue line) isomers; scaling factor was 0.975.

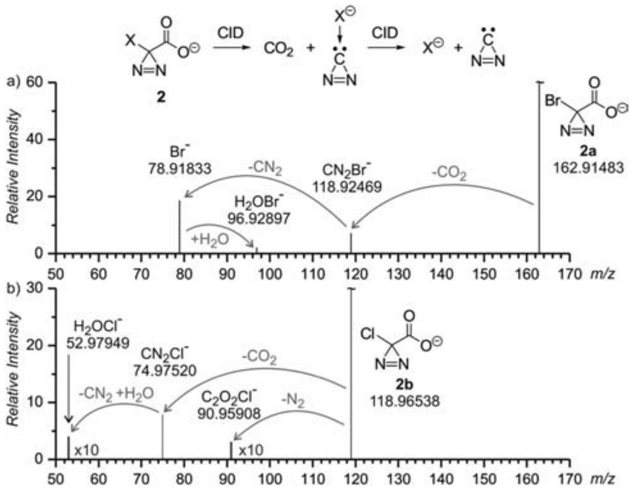


Figure 2. CID spectra of carboxylate ions (a) **2a** and (b) **2b** (^{79}Br and ^{35}Cl isotopomers) obtained using an Orbitrap mass spectrometer. The intensities of the parent ions were normalized to 100 (off-scale); the signals at nominal *m/z* 53 and 91 in (b) are scaled by a factor of 10.

We continued in the characterization of ions **2a** and **2b** by CID with the aim to extract their experimental BDEs for decarboxylation. We have used two fundamentally different mass spectrometers (triple quadrupole and ion trap instruments) and thus two independent approaches for evaluation of the obtained data. The results obtained with the triple quadrupole instrument were evaluated using Chen's L-CID procedure.[17] The energy-dependent CID curves were measured at several collision gas pressures. The obtained threshold energies were extrapolated to zero pressure (see the SI). The dissociation threshold for decarboxylation of the bromo carboxylate **2a** was determined as 22.3 ± 0.4 kcal/mol, and that of the chloro carboxylate **2b** as 27.6 ± 0.3 kcal/mol. These values are in excellent agreement with the predicted BDEs (Table 1). We note in passing that decarboxylation was always accompanied by subsequent dehalogenation, and for the determination of the threshold energy for the CO_2 loss from **2a** and **2b**, the sum of the

Table 1. Calculated and Experimental BDEs[a]

	reaction	calcd[b]	experimental (CID) QOQ[c]	experimental (CID) IT[d]
(1)	**2a** → c-CN_2Br^- + CO_2	24.5	22.3 ± 0.4	19.1 ± 1.2
(2)	**2b** → c-CN_2Cl^- + CO_2	27.8	27.6 ± 0.3	29.6 ± 1.2
(3)	**4a** → CF_2Br^- + CO_2	22.1	20.0 ± 0.1	18.0 ± 0.9
(4)	**4b** → CF_2Cl^- + CO_2	26.3	26.9 ± 0.8	27.6 ± 0.7
(5)	c-CN_2Br^- → ***c*-CN₂** + Br^-	10.1	<8.0[e]	–
(6)	c-CN_2Cl^- → ***c*-CN₂** + Cl^-	13.3	–	–
(7)	CF_2Br^- → CF_2 + Br^-	7.3	–	–
(8)	CF_2Cl^- → CF_2 + Cl^-	10.1	–	–

[a]Values are in kcal/mol. [b]Calculated at the MP4/aug-cc-pVTZ//MP2/6-311+g(d) level (refs 7 and 8). [c]Triple quadrupole. [d]Ion trap. [e]Confidence interval not determined.

corresponding c-CN_2X^- and X^- fragment abundances was evaluated.

Analogous measurements were also performed with the ion trap instrument, and the data were evaluated according to Schröder's procedure.[18] Hence, the energy-dependent CID curves were fitted with sigmoid functions, and the extrapolation of their tangent at the inflex to the baseline gave the threshold energy (see the SI). The calibration of the collision energy scale in the ion trap was made via decarboxylation of trifluoroacetate, dichloroacetate, trichloroacetate, and benzoate ions as standards (Figure 3).[19] The BDEs for decarboxylation of **2a** and **2b** determined using this simple ion-trap approach are 19.1 ± 1.2 and 29.6 ± 1.2 kcal/mol, respectively, in good agreement with those theoretically predicted and obtained from the triple quadrupole experiments (Table 1).

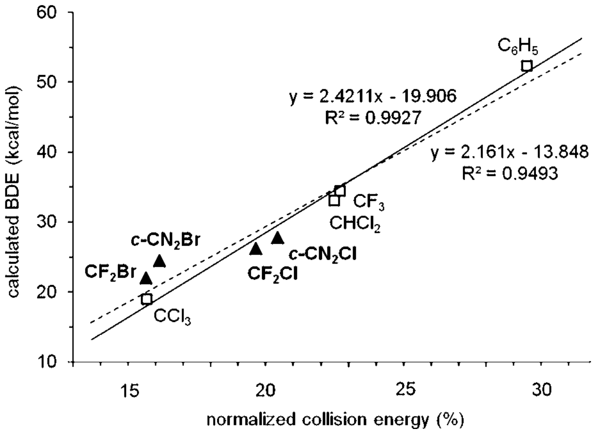


Figure 3. Experimental vs calculated BDEs for decarboxylation of R–COO^- ions. Experimental values were obtained using an ion trap mass spectrometer; calculations were done at the MP4/aug-cc-pVTZ//MP2/6-311+g(d) level (refs 7 and 8). Squares and solid line correspond to calibration species, triangles corresponds to studied species, and the dotted line shows the correlation of all data points.

In order to further confirm the cyclic structure of the CN_2X^- fragment ions, we attempted to generate these species under harder ionization/decarboxylation conditions in the ion source and to determine the energy of their fragmentation to ***c*-CN₂** carbene. This approach was successful only for the bromo derivative **2a** in the triple quadrupole instrument with water as the sheath liquid. The obtained BDE of ***c*-CN₂** in c-CN_2Br^- amounts to less than 8.0 kcal/mol, which is again in very good agreement with theory (Table 1), while the predicted BDEs of the isomeric ^{1}CNN carbene and ^{1}NCN nitrene in the rearranged $BrCNN^-$ and $BrNCN^-$ ions are above 50 and 65 kcal/mol, respectively.[7,8] We have also attempted to determine the BDEs of ***c*-CN₂** in c-CN_2X^- by an MS^3 experiment using the ion trap instrument. The fragment ions were, however, formed with a sufficient internal energy to undergo spontaneous dehalogenation even at zero collision energy.

The very good mutual accordance between the calculated and experimentally determined BDEs allowed us to explore other related systems. Based on calculations we previously predicted remarkable analogies between the electron affinities and ionization potentials of ***c*-CN₂** and the fluoro carbenes FCX (X = F or Cl).[1a] There are also close similarities between the geometries, expected basicities, and BDEs of c-CN_2X^- and CF_2X^- (X = Cl or Br) ions. Thus, we extended our CID experiments to bromodifluoro- and chlorodifluoroacetate ions (**4a** and **4b**), introduced as sodium salts, and we have found that their observed BDEs for the loss of CO_2 indeed closely parallel those of diazirine carboxylates **2a** and **2b**, in very good agreement with theory (Table 1 and Figure 3). In addition, the weakly bonded CF_2X^- ions[20] eluded our experimental determination of the BDE for the loss of CF_2 carbene, likely for the same reasons as given above for the c-CN_2X^-/***c*-CN₂** pair. It should be emphasized that the similar behavior of carboxylates **2** and **4** in our CID experiments can be considered as indirect evidence for the validity of the structural assignments of the c-CN_2X^- and ***c*-CN₂** species.

In summary, we have prepared the novel halodiazirine carboxylic acids **2-H** and their sodium salts **2-Na**. Carboxylate ions **2** underwent the dissociation of CO_2 during CID at low energies, while no competing loss of N_2 was observed for the bromo anion **2a** and only minor denitrogenation occurred with the chloro anion **2b**. The resulting c-CN_2X^- ions readily dissociated to ***c*-CN₂** carbene, and the BDE for c-CN_2Br^- was found to be less than 8 kcal/mol. The related system of difluorohaloacetic carboxylates **4a,b**, CF_2X^- ions, and CF_2 carbene exhibited almost identical behavior, as predicted previously. The structural assignments were based on very good agreement between the calculated and experimental BDEs.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, spectroscopic data for all new compounds, mass spectrometry and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: martinut@vscht.cz.
*E-mail: jana.roithova@natur.cuni.cz.

Author Contributions

‖E.H. and J.V. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the European Research Council (StG ISORI, No: 258299) and the Ministry of Education, Youth, and Sports of the Czech Republic (Specific University Research Grant MSMT 20/2014) is gratefully acknowledged. Mr. Philippe

Maître and Mr. Vincent Steinmetz (CLIO) as well as Ms. Květa Bártová (ICT) are acknowledged for their help and assistance.

■ REFERENCES

(1) (a) Martinů, T.; Böhm, S.; Hanzlová, E. *Eur. J. Org. Chem.* **2011**, 6254. (b) Hanzlová, E.; Navrátil, R.; Čejka, J.; Böhm, S.; Martinů, T. *Org. Lett.* **2014**, *16*, 852.

(2) The previously unpublished reaction of chloro ester **1b** is slower and lower yielding than that of bromo ester **1a**, but both reactions afford the same types of products; see the SI.

(3) The formation of ***c*-CN$_2$** in the gas phase from the diazirinyl anion *c*-CN$_2$H$^-$ has been implicated by S. Kass: (a) Kroeker, R. L.; Kass, S. R. *J. Am. Chem. Soc.* **1990**, *112*, 9024. (b) Tian, Z.; Kass, S. R. *Chem. Rev.* **2013**, *113*, 6986.

(4) TIs of this type are known to be metastable in the gas phase: Haas, G. W.; Giblin, D. E.; Gross, M. L. *Int. J. Mass Spectrom.* **1998**, *172*, 25.

(5) Graul, S. T.; Squires, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 2517.

(6) All calculations in this work have been done using *Gaussian 09*, Revision D.01; Gaussian, Inc.: Wallingford, CT, 2013. See the SI for the complete reference.

(7) BDEs (i.e., loss of CO$_2$ or X$^-$ ion) were obtained as the difference between the sum of electronic energies of completely separated product fragments and the BSSE-corrected energy of a reactant calculated at the MP4 level; all energies include a zero-point correction calculated at the MP2 level.

(8) The wave functions of some species were found to exhibit an RHF → UHF instability at the B3LYP, MP2, MP4, and CCSD(T) levels. We determined using the T$_1$ diagnostic at the CCSD(T)//aug-cc-pVTZ level whether a single-reference-based electron correlation procedure is appropriate for the treatment of such species: Lee, T. J.; Taylor, P. R. *Int. J. Quant. Chem. Symp.* **1989**, *23*, 199. The test was passed ($T_1 < 0.020$) by *c*-CN$_2$Br$^-$ ($T_1 = 0.015$) and *c*-CN$_2$Cl$^-$ ions ($T_1 = 0.016$); their dissociation energies at the CCSD(T) level are nearly identical to those at the MP4 level. On the other hand, the calculated energies of the BrCNN$^-$ ion ($T_1 = 0.021$), ^{1}CNN singlet carbene ($T_1 = 0.026$), and ^{1}NCN singlet nitrene ($T_1 = 0.026$) are expected to be less accurate. The singlet−triplet gap for the latter two species calculated at the MP4 level is, however, still in good agreement with experimental values (within 1 and 4 kcal/mol, respectively), indicating sufficient accuracy of the calculations for our purposes. See the SI for details.

(9) Reactions of **1** with nucleophiles in methanol do not result in the expulsion of the *c*-CN$_2$X moiety (ref 1b).

(10) There is only one other diazirine-3-carboxylic acid (the 3-methyl derivative) reported in the literature: Church, R. F. R.; Weiss, M. J. (American Cyanamid Co., USA). *Substituted diaziridines and diazirines.* U.S. Patent 3,525,736, August 25, 1970.

(11) Ortega, J. M.; Glotin, F.; Prazers, R. *Infrared Phys. Technol.* **2006**, *49*, 133.

(12) Mac Aleese, L.; Maître, P. *Mass Spectrom. Rev.* **2007**, *26*, 583.

(13) Roithová, J. *J. Chem. Soc. Rev.* **2012**, *41*, 547.

(14) Moss, R. A. *Acc. Chem. Res.* **2006**, *39*, 267.

(15) Marek, A.; Tureček, F. *J. Am. Soc. Mass. Spectrom.* **2014**, *25*, 778.

(16) The mass corresponding to the Cl$^-$ ion was below the cutoff of our instrument.

(17) Narancic, S.; Bach, A.; Chen, P. *J. Phys. Chem. A* **2007**, *11*, 7006.

(18) Zins, E. L.; Pepe, C.; Schröder, D. *J. Mass Spectrom.* **2010**, *45*, 1253.

(19) The collision energy in the ion trap instrument is given in % of a "normalized collision energy" scale, and it has to be transformed into standard energy units by a calibration.

(20) (a) Paulino, J. A.; Squires, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 1845. (b) Moss, R. A.; Zhang, M.; Krogh-Jespersen, K. *Org. Lett.* **2009**, *11*, 5702.